Remarks

The present invention relates to intracellular receptors, methods for the modulation thereof, and methods for the identification of novel ligands therefor. In a particular aspect, the present invention relates to members of a family of silencing mediators of retinoic acid and thyroid hormone receptors (SMRT). Invention methods include the identification of compounds which function as ligands (or ligand precursors) for intracellular receptors and compounds which modulate transcription. In another aspect, the present invention relates to novel chimeric constructs and uses therefor.

Claims 1-37 remain currently pending. For the Examiner's convenience, a clean copy of the complete set of all pending claims for this application is also provided in APPENDIX A.

The restriction of claims 1-37 under 35 USC § 121, as allegedly being drawn to seven distinct inventions, is respectfully traversed. Applicants respectfully submit that the claims of Group I (claims 1-25, drawn to nucleic acids, vectors, and host cells), Group II (claims 26-28 and 31-33, drawn to polypeptides), Group III (claims 29 and 30, drawn to antibodies and Groups IV-VII (claims 34-37, drawn to methods of identifying modulating and binding agents) are all interrelated and a prior art search of one group would, of necessity, involve a search of the other groups.

Specifically, the nucleic acid molecules of Group I encode the polypeptides of Group II (see, for example, specification at page 14, lines 23-27). As such, the nucleic acid molecules and polypeptides are capable of use together. As disclosed in the specification, a nucleic acid molecule can be contained in an expression vector and transfected into a host cell to provide a convenient means to prepare the peptide encoded by that nucleic acid molecule (see, for example, specification at page 18, lines 16-23). Similarly, the antibodies of Group III specifically bind to the polypeptides of Group II (see, for example, specification at page 11, lines 27-30). Therefore, the inventions of Groups I, II and III are disclosed as capable of use together, and are thus related.

It is respectfully submitted that claims drawn to uses of the invention SMRT (Groups IV-VII) could readily be regrouped into a smaller number of groups, without adding to the burden on the Examiner.

Thus, for example, Group IV (i.e., claim 34, drawn to a method for identifying an agent that modulates the repressor potential of SMRT) could readily be combined with Group V (i.e., claim 35, drawn to a method for identifying an agent that modulates a SMRT function); with Group VI (i.e., claim 36, drawn to a method of modulating the transcriptional potential of a receptor using SMRT); and with Group VII (i.e., claim 37, drawn to a method of identifying a molecule that interacts with SMRT). Groups IV-VII are thus all drawn to methods for use of the SMRT co-suppressor, and a prior art search of one group would, of necessity, involve a search of the other group.

Indeed, compounds identified by the methods of any of these claims are suitable for use in the other claimed methods as well. Thus, methods of screening for modulators of expression may identify modulators of transcriptional activity or binding agents. In addition, identified modulators of SMRT repressor potential may very well provide information regarding DNA expression from the nuclear receptors where SMRT is repressing transcription. Furthermore, identified binding agents will also provide information regarding SMRT functional activity, and thus in turn, nuclear receptor transcriptional activity.

Therefore, no conservation of PTO resources would be realized if the restriction requirement into seven Groups is maintained. Accordingly, reconsideration and withdrawal of the restriction requirement are respectfully requested. Alternatively, regrouping of the claims into fewer groups as suggested above is respectfully requested.

However, in order to be fully responsive, Applicants elect the Group I claims (i.e., claims 1-25, drawn to nucleic acids, vectors and host cells encompassing SMRT) with traverse. Claims 26-37 are retained herein pending final disposition of the elected claims.

The further assertion that the application allegedly contains claims directed to patentably distinct species is respectfully traversed. Applicants respectfully submit that species a. (human SMRT; SEQ ID NOs: 4 and 5), species b. (mouse SMRTα; SEQ ID NOs: 6 and 7), and species c. (mouse SMRTβ; SEQ ID NOs: 8 and 9) are all variants of the claimed SMRT nucleic acid and encoded proteins. Figure 4 provides a computerized alignment of the amino acid sequence of the three species as exemplary SMRT co-repressors. Large regions of homology show that the human and mouse SMRT variants are intimately related. Thus, a prior art search of one group would, of necessity, involve a search of the other groups.

However, in order to be fully responsive, Applicants elect species a. (i.e., human SMRT; SEQ ID NOs: 4 and 5) with traverse. Claims 1-7, 14-16 and 18-37 are readable on the elected species. Claims 8-13 and 17 are retained herein pending final disposition of claims readable on the elected species.

Conclusion

In view of the above remarks, reconsideration of the restriction requirement and the election of species, and prompt and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosure: Appendix A

APPENDIX A – COMPLETE SET OF PENDING CLAIMS

1. An isolated polynucleotide encoding a member of a family of silencing mediators of retinoic acid receptor and thyroid hormone receptor, or an isoform or peptide portion thereof (SMRT co-repressor), or an isolated polynucleotide complementary thereto.

2. The polynucleotide of claim 1, which modulates transcriptional potential of a member of the nuclear receptor superfamily (nuclear receptor).

3. The polynucleotide of claim 2, wherein the SMRT co-repressor comprises a repression domain having

a) less than about 83% identity with a Sin3A interaction domain of N-CoR set forth as amino acids 255 to 312 of SEQ ID NO: 11;

b) less than about 57% identity with repression domain 1 of N-CoR set forth as amino acids 1 to 312 of SEQ ID NO: 11;

c) less than about 66% identity with a SANT domain of N-CoR set forth as amino acids 312 to 668 of SEQ ID NO: 11; or

d) less than about 30% identity with repression domain 2 of N-CoR set forth as amino acids 736 to 1031 of SEQ ID NO: 11,

and polynucleotides that hybridize thereto under stringent conditions.

4. The polynucleotide of claim 1, wherein the SMRT co-repressor is a human SMRT co-repressor having an amino acid sequence as set forth in SEQ ID NO: 5 or conservative variations thereof.

5. A polynucleotide which hybridizes under stringent conditions with a polynucleotide according to claim 2.

6. A polynucleotide that has at least 80% sequence identity with a polynucleotide according to claim 2.

7. The polynucleotide of claim 4, which has a nucleotide sequence as set forth in SEQ ID NO: 4, and conservative variations thereof.

8. The polynucleotide of claim 1, wherein the SMRT co-repressor is a mouse SMRTα isoform.

9. The polynucleotide of claim 6, having an amino acid sequence as set forth in SEQ ID NO: 7 or conservative variations thereof.

10. The polynucleotide of claim 4. which has a nucleotide sequence as set forth in SEQ ID NO: 6.

11. The polynucleotide of claim 1, wherein the SMRT co-repressor is a mouse SMRTβ isoform.

12. The polynucleotide of claim 11, having an amino acid sequence as set forth in SEQ ID NO: 9 or conservative variations thereof.

13. The polynucleotide of claim 11, which has a nucleotide sequence as set forth in SEQ ID NO: 8.

14. The polynucleotide of claim 1, comprising a nucleotide sequence selected from the group consisting of:

nucleotides 1 to 3094 of SEQ ID NO: 4;

nucleotides 1 to 3718 of SEQ ID NO: 6; and

nucleotides 1 to 2801 of SEQ ID NO: 8.

15. A polynucleotide that under stringent conditions with a polynucleotide according to claim 14, provided that the polynucleotide does not contain a sequence identical to SEQ ID NO: 11.

16. A polynucleotide that has at least 80% sequence identity with a polynucleotide according to claim 14, provided that the polynucleotide does not contain a sequence identical to SEQ ID NO: 11.

17. A polynucleotide of claim 1, comprising a nucleotide sequence selected from the group consisting of:

nucleotides 1 to 8388 of SEQ ID NO: 6; and

nucleotides 1 to 7465 of SEQ ID NO: 8.

18. The polynucleotide of claim 1, comprising nucleotides 1 to 8561 of SEQ ID NO: 4.

19. The polynucleotide of claim 1, which is operably linked to a second nucleotide sequence.

20. The polynucleotide of claim 19, which encodes a fusion polypeptide comprising the SMRT co-repressor operably linked to a DNA binding domain of a transcription factor.

21. A vector comprising the polynucleotide of claim 1.

22. A host cell containing the polynucleotide of claim 1.

23. An isolated oligonucleotide, comprising at least 15 nucleotides that can hybridize specifically to the polynucleotide of claim 1, but not to a polynucleotide encoding SEQ ID NO: 11 or to a polynucleotide encoding an amino acid sequence consisting of amino acids 1031 to 2517 of SEQ ID NO: 5.

24. The oligonucleotide of claim 23, wherein the polynucleotide encodes at least five contiguous amino acids of a sequence selected from the group consisting of:

amino acids 720 to 745 of SEQ ID NO: 5;

amino acids 716 to 742 of SEQ ID NO: 7; and

amino acids 497 to 523 of SEQ ID NO: 9.

25. The oligonucleotide of claim 23, which can hybridize specifically to a polynucleotide encoding SEQ ID NO: 5 or SEQ ID NO: 7, but not to a polynucleotide encoding SEQ ID NO: 9.

26. An isolated silencing mediator of retinoic acid and thyroid hormone receptor, or isoform or peptide portion thereof (SMRT co-repressor), wherein the co-repressor modulates transcriptional potential of a member of the nuclear receptor superfamily (nuclear receptor).

27. An isolated co-repressor comprising a repression domain having

a) less than about 83% identity with a Sin3A interaction domain of N-CoR set forth as amino acids 255 to 312 of SEQ ID NO: 11;

b) less than about 57% identity with repression domain 1 of N-CoR set forth as amino acids 1 to 312 of SEQ ID NO: 11;

c) less than about 66% identity with a SANT domain of N-CoR set forth as amino acids 312 to 668 of SEQ ID NO: 11; or

d) less than about 30% identity with repression domain 2 of N-CoR set forth as amino acids 736 to 1031 of SEQ ID NO: 11.

28. An isolated peptide, comprising at least six contiguous amino acids of an amino acid sequence selected from the group consisting of:

amino acids 1 to 1030 of SEQ ID NO: 5;

amino acids 1 to 1029 of SEQ ID NO: 7;

amino acids 1 to 809 of SEQ ID NO: 9;

and conservative variations thereof,

provided the peptide is not identical to a sequence of SEQ ID NO: 11.

29. An isolated antibody that binds specifically to the peptide of claim 28.

30. A cell line, which produces the antibody of claim 29.

31. A chimeric molecule, comprising the SMRT co-repressor of claim 26 and at least a second molecule.

32. A complex, comprising a SMRT co-repressor of claim 26 and a member of the nuclear receptor superfamily (nuclear receptor).

33. The complex of claim 32, wherein the nuclear receptor is in the form of a dimer.

34. A method for identifying an agent that modulates the repressor potential of a SMRT co-repressor, the method comprising:

a) contacting a host cell with an agent,

wherein the host cell contains a first expressible nucleotide sequence operably linked to a first DNA regulatory element, and

expresses a fusion polypeptide comprising a SMRT co-repressor of claim 26, and a DNA binding domain of a first transcription factor, which can specifically bind the first DNA regulatory element,

and wherein binding of the DNA binding domain of the first transcription factor to the first DNA regulatory element results in expression of the first expressible nucleotide sequence; and

b) detecting a change in the level of expression of the first expressible nucleotide sequence due to contacting the host cell with the agent, thereby identifying an agent that modulates the repressor potential of a SMRT co-repressor.

35. A method for identifying an agent that modulates a function of a SMRT co-repressor, the method comprising:

a) contacting a SMRT co-repressor of claim 26,

a member of the nuclear receptor superfamily (nuclear receptor), and

an agent; and

b) detecting an altered activity of the SMRT co-repressor in the presence of the agent as compared to the absence of the agent, thereby identifying an agent that modulates a function of the SMRT co-repressor.

36. A method of modulating the transcriptional potential of a member of the nuclear receptor superfamily (nuclear receptor) in a cell, the method comprising introducing a polynucleotide of claim 1 into the cell, whereby the polynucleotide or an expression product of the polynucleotide alters the level of a SMRT co-repressor in the cell, thereby modulating the transcriptional potential of the nuclear receptor.

37. A method of identifying a molecule that interacts specifically with a SMRT co-repressor, the method comprising:

a) contacting the molecule with the SMRT co-repressor of claim 26; and

b) detecting specific binding of the molecule to the SMRT co-repressor, thereby identifying a molecule that interacts specifically with a SMRT co-repressor.